17616(AP)

CYCLOPENTANE HEPTAN(ENE)OIC ACID, 2-THIOCARBAMOYLOXY AND 2-CARBAMOYLOXY COMPOUNDS AS THERAPEUTIC AGENTS

Background of the Invention

1. Field of the Invention

The present invention relates to cyclopentane heptanoic acid, 2-thiocarbamoyloxy and 2-carbamoyloxy compounds which are substituted in the 9-position with oxo or halogen groups, e.g. fluoro or chloro groups. These compounds are ocular hypotensives and may be suited for the management of glaucoma.

2. Description of Related Art

Ocular hypotensive agents are useful in the treatment of a number of various ocular hypertensive conditions, such as post-surgical and post-laser trabeculectomy ocular hypertensive episodes, glaucoma, and as presurgical adjuncts.

Glaucoma is a disease of the eye characterized by increased intraocular pressure. On the basis of its etiology, glaucoma has been classified as primary or secondary. For example, primary glaucoma in adults (congenital glaucoma) may be either open-angle or acute or chronic angle-closure. Secondary glaucoma results from pre-existing ocular diseases such as uveitis, intraocular tumor or an enlarged cataract.

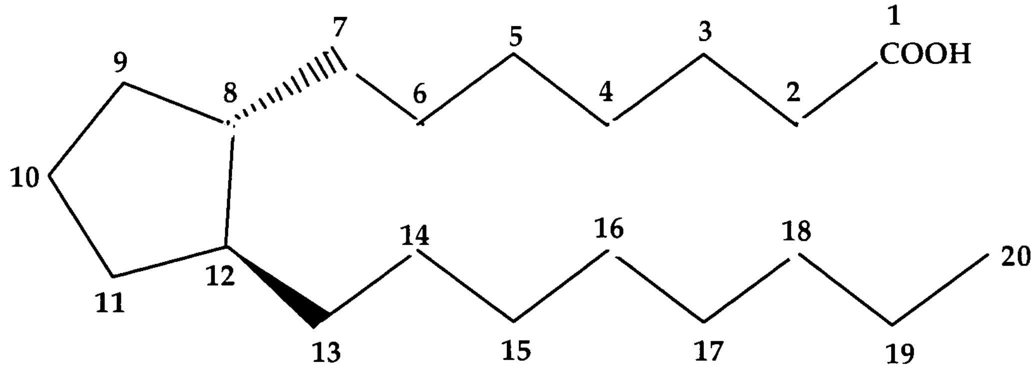
The underlying causes of primary glaucoma are not yet known. The increased intraocular tension is due to the obstruction of aqueous humor outflow. In chronic open-angle glaucoma, the anterior chamber and its anatomic structures appear normal, but drainage of the aqueous humor is impeded. In acute or chronic angle-closure glaucoma, the anterior chamber is shallow, the filtration angle is narrowed, and the iris may obstruct the trabecular meshwork at the entrance of the canal of Schlemm. Dilation of the pupil may push the root of the iris forward against the angle, and may

produce pupilary block and thus precipitate an acute attack. Eyes with narrow anterior chamber angles are predisposed to acute angle-closure glaucoma attacks of various degrees of severity.

Secondary glaucoma is caused by any interference with the flow of aqueous humor from the posterior chamber into the anterior chamber and subsequently, into the canal of Schlemm. Inflammatory disease of the anterior segment may prevent aqueous escape by causing complete posterior synechia in iris bombe, and may plug the drainage channel with exudates. Other common causes are intraocular tumors, enlarged cataracts, central retinal vein occlusion, trauma to the eye, operative procedures and intraocular hemorrhage.

Considering all types together, glaucoma occurs in about 2% of all persons over the age of 40 and may be asymptotic for years before progressing to rapid loss of vision. In cases where surgery is not indicated, topical b-adrenoreceptor antagonists have traditionally been the drugs of choice for treating glaucoma.

Certain eicosanoids and their derivatives have been reported to possess ocular hypotensive activity, and have been recommended for use in glaucoma management. Eicosanoids and derivatives include numerous biologically important compounds such as prostaglandins and their derivatives. Prostaglandins can be described as derivatives of prostanoic acid which have the following structural formula:



Various types of prostaglandins are known, depending on the structure and substituents carried on the alicyclic ring of the prostanoic acid skeleton. Further classification is based on the number of unsaturated bonds in the side chain indicated by numerical subscripts after the generic type of prostaglandin [e.g. prostaglandin E_1 (PGE_1), prostaglandin E_2 (PGE_2)], and on the configuration of the substituents on the alicyclic ring indicated by α or β [e.g. prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$)].

Prostaglandins were earlier regarded as potent ocular hypertensives, however, evidence accumulated in the last decade shows that some prostaglandins are highly effective ocular hypotensive agents, and are ideally suited for the long-term medical management of glaucoma (see, for example, Bito, L.Z. <u>Biological Protection with Prostaglandins</u>, Cohen, M.M., ed., Boca Raton, Fla, CRC Press Inc., 1985, pp. 231-252; and Bito, L.Z., <u>Applied Pharmacology in the Medical Treatment of Glaucomas</u> Drance, S.M. and Neufeld, A.H. eds., New York, Grune & Stratton, 1984, pp. 477-505. Such prostaglandins include $PGF_{2\alpha}$, $PGF_{1\alpha}$, PGE_2, and certain lipid-soluble esters, such as C_1 to C_2 alkyl esters, e.g. 1-isopropyl ester, of such compounds.

Although the precise mechanism is not yet known experimental results indicate that the prostaglandin-induced reduction in intraocular pressure results from increased uveoscleral outflow [Nilsson et. al., <u>Invest. Ophthalmol. Vis. Sci.</u> (suppl), 284 (1987)].

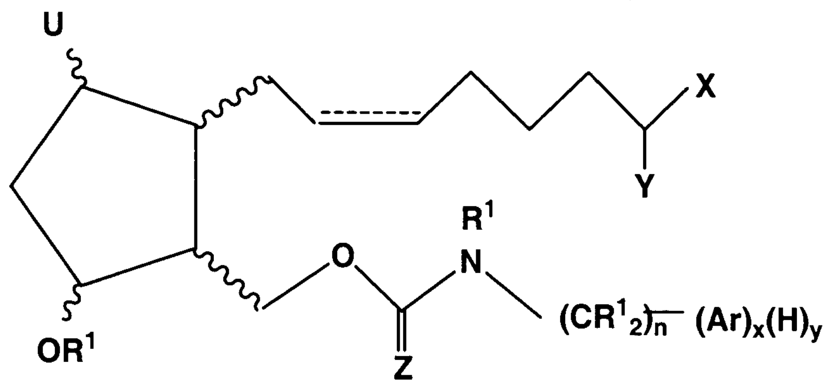
The isopropyl ester of $PGF_{2\alpha}$ has been shown to have significantly greater hypotensive potency than the parent compound, presumably as a result of its more effective penetration through the cornea. In 1987, this compound was described as "the most potent ocular hypotensive agent ever reported" [see, for example, Bito, L.Z., Arch. Ophthalmol. 105, 1036 (1987), and Siebold et. al., Prodrug 5 3 (1989)].

Whereas prostaglandins appear to be devoid of significant intraocular side effects, ocular surface (conjunctival) hyperemia and foreign-body sensation have been consistently associated with the topical ocular use of such compounds, in particular $PGF_{2\alpha}$ and its prodrugs, e.g., its 1-isopropyl ester, in humans. The clinical potentials of prostaglandins in the management of conditions associated with increased ocular pressure, e.g. glaucoma are greatly limited by these side effects.

In a series of co-pending United States patent applications assigned to Allergan, Inc. prostaglandin esters with increased ocular hypotensive activity accompanied with no or substantially reduced side-effects are disclosed. The co-pending USSN 596,430 (filed 10 October 1990, now U.S. Patent 5,446,041), relates to certain 11-acyl-prostaglandins, such as 11-pivaloyl, 11-acetyl, 11-isobutyryl, 11-valeryl, and 11-isovaleryl $PGF_{2\alpha}$. Intraocular pressure reducing 15-acyl prostaglandins are disclosed in the co-pending application USSN 175,476 (filed 29 December 1993). Similarly, 11,15-9,15 and 9,11-diesters of prostaglandins, for example 11,15-dipivaloyl $PGF_{2\alpha}$ are known to have ocular hypotensive activity. See the co-pending patent applications USSN Nos. 385,645 (filed 07 July 1989, now U.S. Patent 4,994,274), 584,370 (filed 18 September 1990, now U.S. Patent 5,028,624) and 585,284 (filed 18 September 1990, now U.S. Patent 5,034,413). The disclosures of all of these patent applications are hereby expressly incorporated by reference.

Summary of the Invention

The present invention provides cyclopentane heptan(ene)oic acid, 2 thiocarbamoyloxy and 2-carbamoyloxy compounds which may be useful for treating ocular hypertension and are represented by formula I



wherein a wavy segment represents an α or β bond; the dashed line represents a double bond or a single bond; U is = O,

or

wherein W is halogen, e.g. fluoro or chloro; Z is O or S; Ar is an aryl or hetero aryl radical having from 4 to 10 carbon atoms, e.g. phenyl, furyl, thienyl, etc. or substituted aryl or a substituted heteroaryl radical; n is 0 or an integer of from 1 to 4; x and y are 1 or 0, provided that when x is 1, y is 0 and when x is 0, y is 1; R^1 is hydrogen or a lower alkyl radical or a substituted lower alkyl radical having up to six carbon atoms; X is selected from the group consisting of $-OR^1$ and $-N(R^1)_2$; Y is = O or represents 2 hydrogen radicals and the 9 esters thereof, e.g. the lower alkyl esters having up to six carbon atoms; and/or the pharmaceutically acceptable salts of said compound and/or the esters thereof. In particular, the substituents on the

lower alkyl, aryl or heteroaryl radical may be selected from the group consisting of lower alkyl, e.g. C_1 to C_6 alkyl; hydroxy; lower alkyloxy, e.g. OCH_3; halogen, e.g. fluoro, chloro and bromo; trifluoromethyl (CF_3); COR^1, e.g. $COCH_3$; $COCF_3$; SO_2NR^1, e.g. SO_2NH_2; NO_2; CN; etc.

In a further aspect, the present invention relates to an ophthalmic solution comprising a therapeutically effective amount of a compound of formula (I), wherein the symbols have the above meanings, or a pharmaceutically acceptable salt thereof, in admixture with a non-toxic, ophthalmically acceptable liquid vehicle, packaged in a container suitable for metered application.

In a still further aspect, the present invention relates to a pharmaceutical product, comprising

a container adapted to dispense its contents in a metered form; and

an ophthalmic solution therein, as hereinabove defined.

Brief Description of the Drawing Figures

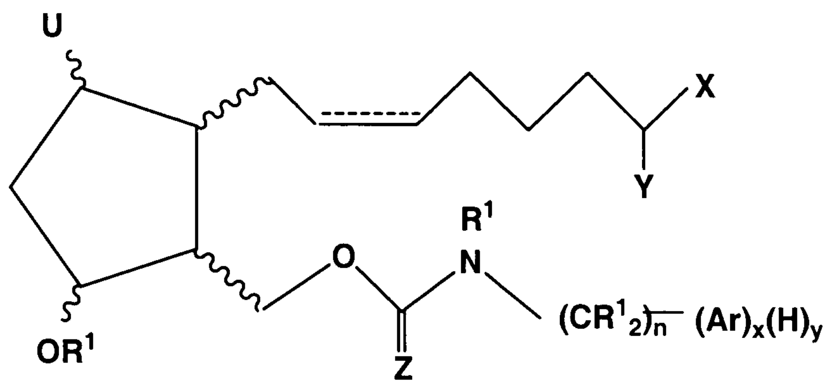
FIG. 1 is a schematic of the chemical synthesis of certain compounds of the invention, specifically certain 9-keto compounds disclosed in Examples 1 through 7 below.

FIG. 2 is a schematic of the chemical synthesis of certain compounds of the invention, specifically certain 9-chloro compounds disclosed in Examples 3 and 4, below.

FIG. 3 is a schematic of the chemical synthesis of certain compounds of the invention, specifically certain thiocarbamoyloxy compounds disclosed in Examples 7 and 8, below.

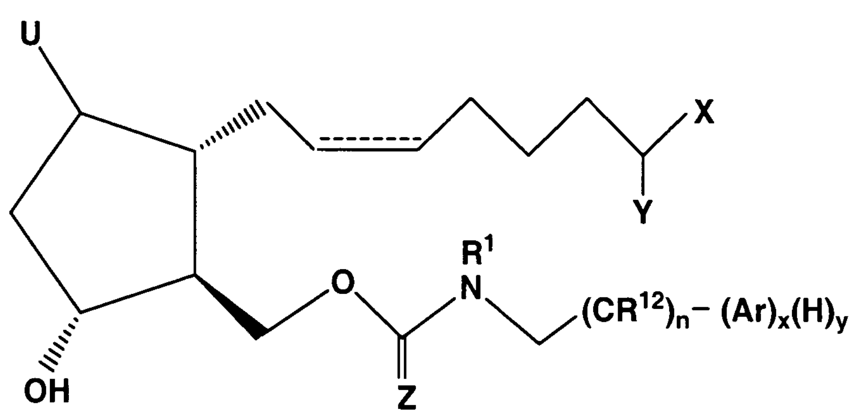
Detailed Description of the Invention

The present invention relates to cyclopentane heptan(ene)oic acid, 2-thiocarbamoyloxy and 2-carbamoyloxy compounds encompassed by the following structural formula I:



wherein the substituents and symbols are as hereinabove defined. The dotted line on the bond between carbons 5 and 6 (C-5) indicates a single or double bond. If two solid lines are used at C-5, it indicates a specific configuration for that double bond.

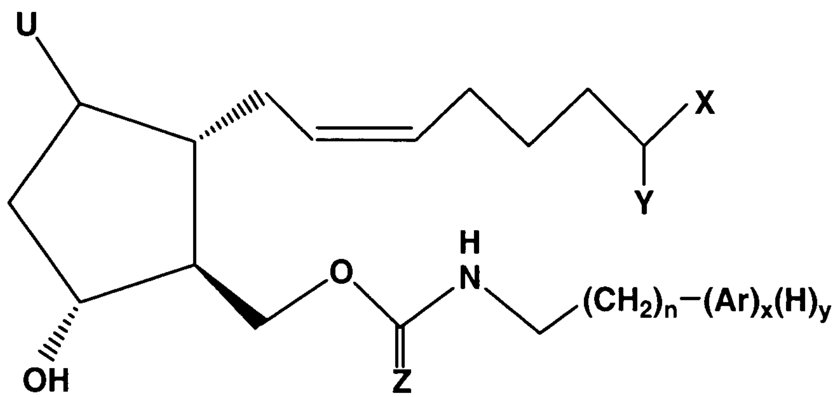
A preferred group of the compounds of the present invention includes compounds that have the following structural formula II:



wherein n is 0 or 1, 2 or 4; hatched lines at position C-8 and C-11 indicate the α configuration; and the triangle at position C-12 represents β orientation. Preferably Y is = O.

More preferably, Ar is selected from the group consisting of phenyl, furyl and thienyl.

Another preferred group includes compounds having the formula III:



In compounds of formula III, preferably X is $-OR^1$ or $N(R^1)_2$ and Y is = O, e.g. the 1-position is a carboxylic acid or carboxylamide radical.

Preferably, R^1 is H or CH_3.

Preferably n is 3 and y is 1.

Preferably Ar is phenyl, thienyl, chlorophenyl or trifluoromethyl phenyl.

Preferably X is OH.

Preferably Y is = O.

Preferably U is = O or

The above compounds of the present invention may be prepared by methods that are known in the art or according to the working examples

below. The compounds, below, are especially preferred representative of the compounds of the present invention.

(Z)-7-((1R,2S,3R)-2-Butylcarbamoyloxymethyl-3-hydroxy-5-oxo-cyclopentyl)-hept-5-enoic acid methyl ester

(Z)-7-((1R,2S,3R)-2-Butylcarbamoyloxymethyl-3-hydroxy-5-oxo-cyclopentyl)-hept-5-enoic acid

(Z)-7-((1R,2S,3R,5R)-2-Butylcarbamoyloxymethyl-5-chloro-3-hydroxy-cyclopentyl)-hept-5-enoic acid methyl ester

(Z)-7-((1R,2S,3R,5R)-2-Butylcarbamoyloxymethyl-5-chloro-3-hydroxy-cyclopentyl)-hept-5-enoic acid

(Z)-7-((1R,2S,3R)-3-Hydroxy-5-oxo-2-phenethylcarbamoyloxymethyl-cyclopentyl)-hept-5-enoic acid methyl ester

(Z)-7-((1R,2S,3R)-3-Hydroxy-5-oxo-2-phenethylcarbamoyloxymethyl-cyclopentyl)-hept-5-enoic acid

(Z)-7-((1R,2S,3R)-2-Butylthiocarbamoyloxymethyl-3-hydroxy-5-oxo-cyclopentyl)-hept-5-enoic acid methyl ester

(Z)-7-((1R,2S,3R)-2-Butylthiocarbamoyloxymethyl-3-hydroxy-5-oxo-cyclopentyl)-hept-5-enoic acid

A pharmaceutically acceptable salt is any salt which retains the activity of the parent compound and does not impart any deleterious or undesirable effect on the subject to whom it is administered and in the context in which it is administered. Of particular interest are salts formed with inorganic ions, such as sodium, potassium, calcium, magnesium and zinc.

Pharmaceutical compositions may be prepared by combining a therapeutically effective amount of at least one compound according to the present invention, or a pharmaceutically acceptable acid addition salt thereof, as an active ingredient, with conventional ophthalmically acceptable pharmaceutical excipients, and by preparation of unit dosage forms suitable for topical ocular use. The therapeutically efficient amount typically is between about 0.0001 and about 5% (w/v), preferably about 0.001 to about 1.0% (w/v) in liquid formulations.

For ophthalmic application, preferably solutions are prepared using a physiological saline solution as a major vehicle. The pH of such ophthalmic solutions should preferably be maintained between 6.5 and 7.2 with an appropriate buffer system. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

Preferred preservatives that may be used in the pharmaceutical compositions of the present invention include, but are not limited to, benzalkonium chloride, chlorobutanol, thimerosal, phenylmercuric acetate and phenylmercuric nitrate. A preferred surfactant is, for example, Tween 80. Likewise, various preferred vehicles may be used in the ophthalmic preparations of the present invention. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose and purified water.

Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium

chloride, mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. Accordingly, buffers include acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

In a similar vein, an ophthalmically acceptable antioxidant for use in the present invention includes, but is not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

Other excipient components which may be included in the ophthalmic preparations are chelating agents. The preferred chelating agent is edentate disodium, although other chelating agents may also be used in place or in conjunction with it.

The ingredients are usually used in the following amounts:

Ingredient	Amount (% w/v)
active ingredient	about 0.001-5
preservative	0-0.10
vehicle	0-40
tonicity adjustor	1-10
buffer	0.01-10
pH adjustor	q.s. pH 4.5-7.5
antioxidant	as needed
surfactant	as needed
purified water	as needed to make 100%

The actual dose of the active compounds of the present invention depends on the specific compound, and on the condition to be treated; the selection of the appropriate dose is well within the knowledge of the skilled artisan.

The ophthalmic formulations of the present invention are conveniently packaged in forms suitable for metered application, such as in

containers equipped with a dropper, to facilitate the application to the eye. Containers suitable for dropwise application are usually made of suitable inert, non-toxic plastic material, and generally contain between about 0.5 and about 15 ml solution.

The invention is further illustrated by the following non-limiting Examples, which are summarized in the reaction scheme of FIGS. 1 through 3, wherein like numbers refer to the same compounds.

Example 1

(Z)-7-((1R,2S,3R)-2-Butylcarbamoyloxymethyl-3-hydroxy-5-oxo-cyclopentyl)-hept-5-enoic acid methyl ester (6a, Figure 1)

Step 1: Carbamoylation of **1** to give **2a**.

1,4-Diazabicyclo[2.2.2]octane (153 mg, 1.36 mmol) and butyl isocyanate (190 μL, 1.71 mmol) were added sequentially to a solution of **1** (500 mg, 1.13 mmol) in THF (7.5 mL) at rt under nitrogen. The mixture was heated at reflux for 18 h, then cooled and concentrated in vacuo. Purification of the crude residue by flash column chromatography on silica gel (40% EtOAc/hexane) afforded 580 mg (95%) of carbamate **2**.

Step 2: Deprotection of **2a** to give **3a**.

Pyridinium *p*-toluenesulfonate (PPTs, 27 mg, 0.11 mmol) was added to a solution of **2a** (571 mg, 1.06 mmol) in methanol (11 mL) at rt under nitrogen. The solution was heated at 50 °C for 18 h, then cooled and concentrated in vacuo. Purification of the crude residue by flash column chromatography on silica gel (75% → 85% EtOAc/hexane, gradient) afforded 382 mg (97%) of diol **3a**.

Step 3: Silylation of **3a** to give **4a**.

Triethylamine (210 μL, 1.50 mmol), 4-(dimethylamino)pyridine (24 mg, 0.20 mmol), and *tert*-butyldimethylsilyl chloride (166 mg, 1.10 mmol) were sequentially added to a solution of **3a** (372 mg, 1.00 mmol) in CH_2Cl_2 (5.0 mL). The resulting solution was stirred at rt under nitrogen for 20 h. The reaction mixture was then concentrated in vacuo, the saturated aqueous NH_4Cl (50 mL) was added and the mixture was extracted with EtOAc (3x100 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the crude residue by flash column chromatography on silica gel (30% EtOAc/hexane) afforded 278 mg (57%) of desired product **4a**.

Step 4: Oxidation of **4a** to give **5a**.

4-Methylmorpholine *N*-oxide (18 mg, 0.15 mmol) and 4 Å molecular sieves (25 mg) were added to a solution of **4a** (50 mg, 0.10 mmol) in CH_2Cl_2 (0.5 mL). The mixture was cooled to 0 °C and tetrapropylammonium perruthenate (TPAP, 1.8 mg, 0.005 mmol) was added in one portion. The reaction mixture was allowed to warm to rt. After 6 h at rt the reaction was concentrated in vacuo. Purification of the crude residue by flash column chromatography on silica gel (30% EtOAc/hexane) afforded 12 mg (24%) of **5a**.

Step 5: Deprotection of **5a** to give **6a**.

HF-pyridine (50 μL) was added to a solution of **5a** (12 mg, 0.025 mmol) in CH_3CN (0.5 mL) in a plastic scintillation vial at rt. After 18 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with EtOAc (3x5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the crude residue by flash column chromatography on silica gel (30% EtOAc/hexane) afforded 9 mg (98%) of the title compound (**6a**).

Example 2

(Z)-7-((1R,2S,3R)-2-Butylcarbamoyloxymethyl-3-hydroxy-5-oxo-cyclopentyl)-hept-5-enoic acid (7a, Figure 1)

Rabbit liver esterase (134 units/mg, 1 mg) was added to a solution of **6a** (8.0 mg, 0.022 mmol) in MeCN (0.1 mL) and pH 7.2 buffer (1.0 mL). After stirring at rt for 18 h, the reaction mixture was extracted with EtOAc (3x5 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the crude residue by flash column chromatography on silica gel (90% EtOAc/hexane → 100% EtOAc, gradient) afforded 1.8 mg (23%) of **7a**.

Example 3

(Z)-7-((1R,2S,3R,5R)-2-Butylcarbamoyloxymethyl-5-chloro-3-hydroxy-cyclopentyl)-hept-5-enoic acid methyl ester (10, Figure 2)

Step 1: Mesylation of **4a** to give **8a**.

Triethylamine (43 μL, 0.31 mmol) and methanesulfonyl chloride (20 μL, 0.25 mmol) were added sequentially to a solution of **4a** (99 mg, 0.20 mmol) in CH_2Cl_2 (1.5 mL) at rt. After 20 h at rt, saturated aqueous $NaHCO_3$ (10 mL) was added and the mixture was extracted with EtOAc (3x25 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the crude residue by flash column chromatography on silica gel (30% EtOAc/hexane) afforded 45 mg (39%) of **8a**.

Step 2: Conversion of **8a** to chloride **9a**.

Tetrabutylammonium chloride (222 mg, 0.80 mmol) was added to a solution of **8a** (45 mg, 0.080 mmol) in toluene (2.6 mL). The reaction mixture was heated at 40 °C for 18 h after which time thin layer chromatography (TLC) analysis indicated much of the starting mesylate remained. The reaction mixture was heated

to 60 °C for 6 h after which time the reaction was complete by TLC analysis. The cooled mixture was diluted with brine (10 mL) and extracted with EtOAc (3x20 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the crude residue by flash column chromatography on silica gel (15% EtOAc/hexane) afforded 13 mg (32%) of **9a**.

Step 3. Deprotection of **9a** to give **10a**.

The product of step 2 (**9a**, 13 mg, 0.026 mmol) was converted to the title compound (**10a**, 9.3 mg (93%)) in accordance with the procedure in Example 1 (step 5).

Example 4

(Z)-7-((1R,2S,3R,5R)-2-Butylcarbamoyloxymethyl-5-chloro-3-hydroxy-cyclopentyl)-hept-5-enoic acid (11a, Figure 2)

The product of Example 3 (**10a**, 7.8 mg, 0.020 mmol) was converted to the title compound (**11a**, 2.0 mg (27%)) in accordance with the procedure in Example 2.

Example 5

(Z)-7-((1R,2S,3R)-3-Hydroxy-5-oxo-2-phenethylcarbamoyloxymethyl-cyclopentyl)-hept-5-enoic acid methyl ester (6b, Figure 1)

The title compound was prepared in accordance with the procedures of Example 1, replacing butyl isocyanate with phenethyl isocyanate.

Example 6

(Z)-7-((1R,2S,3R)-3-Hydroxy-5-oxo-2-phenethylcarbamoyloxymethyl-cyclopentyl)-hept-5-enoic acid (7b, Figure 1)

The product of Example 5 (**6b**,11 mg, 0.026 mmol) was converted to the title compound (**7b**, 3.1 mg (29%)) in accordance with the procedure of Example 2.

Example 7

(Z)-7-((1R,2S,3R)-2-Butylthiocarbamoyloxymethyl-3-hydroxy-5-oxo-cyclopentyl)-hept-5-enoic acid methyl ester (6c, Figure 1)

The title compound was prepared in accordance with the procedures of Example 1 (steps 1, 2, 3 and 5), replacing butyl isocyanate with phenethyl isothiocyanate and using an different oxidant in step 4 as detailed below (see Figure 3).

Step 4: Oxalyl chloride (2.0 M in CH_2Cl_2, 80 μL, 0.16 mmol) was added to a flask containing CH_2Cl_2 (1.5 mL). The resulting solution was cooled to –78 °C and DMSO (24 μL, 0.34 mmol) was added. After 15 min at –78 °C, **4c** (67 mg, 0.13 mmol) was added as a solution in CH_2Cl_2 (0.5 mL) via cannula. After 1 h at –78 °C, triethylamine (150 μL, 1.08 mmol) was added and the reaction was allowed to warm to rt. After 1 h, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (20 mL) and the resulting mixture was extracted with CH_2Cl_2 (3x30 mL). The extracts were washed with 1 N HCl (20 mL), saturated aqueous $NaHCO_3$ (20 mL) and brine then dried (Na_2SO_4), filtered and concentrated in vacuo. Purification of the crude residue by flash column chromatography on silica gel (20% EtOAc/hexane) afforded 32 mg (48%) of **5c**.

Example 8

(Z)-7-((1R,2S,3R)-2-Butylthiocarbamoyloxymethyl-3-hydroxy-5-oxo-cyclopentyl)-hept-5-enoic acid (7c, Figure 1)

The product of Example 7 (**6c**, 6 mg, 0.016 mmol) was converted to the title product (**7c**, 1.0 mg (17%)) in accordance with the procedure of Example 2.

Potential therapeutic applications for the compounds of the present invention are in osteoporosis, constipation, renal disorders, sexual dysfunction, baldness and in disorder of immune regulation.

The compounds of the invention may also be useful in the treatment of various pathophysiological diseases including acute myocardial infarction, vascular thrombosis, hypertension, pulmonary hypertension, ischemic heart disease, congestive heart failure, and angina pectoris, in which case the compounds may be administered by any means that effect vasodilation and thereby relieve the symptoms of the disease. The compounds of this invention are EP receptor agonists and therefore may be useful, also, for prevention and/or treatment of the following diseases:

acute hepatitis, asthma, bronchitis, burn, chronic obstructive respiratory diseases, Crohn's disease, digestive ulcer, glaucoma (and other diseases related to elevated intraocular pressure), hemophagous syndrome, hepatopathy, hypercytokinemia at dialysis, hypertension, immunological diseases (autoimmune diseases, organ transplantation, etc.), inflammation (such as rheumatoid arthritis), Kawasaki disease, liver injury, macrophage activation syndrome, myocardial ischemia, nephritis, nerve cell death, osteoporosis and diseases associated with bone disorders, premature birth, pulmonary emphysema, pulmonary fibrosis, pulmonary injury, renal failure, sepsis, sexual dysfunction, shock, sleep disorder, Still disease, stomatitis , systemic granuloma, systemic inflammatory syndrome, thrombosis and stroke, ulcerative colitis

For example, administration may be by oral, transdermal, parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, transdermal, or buccal routes.

The compounds of the invention may be used alone, or in combination with other of the known vasodilator drugs.

The compounds of the invention may be formulated into an ointment containing about 0.10 to 10% of the active ingredient in a suitable base of, for example, white petrolatum, mineral oil and petrolatum and lanolin alcohol. Other suitable bases will be readily apparent to those skilled in the art.

The pharmaceutical preparations of the present invention are manufactured in a manner which is itself known, for example, by means of conventional dissolving or suspending the compounds, which are all either water soluble or suspendable. For administration in the treatment of the other mentioned pathophysiological disorders. The pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer such as glycerol or sorbitol. The push-fit capsules can contain the active compounds in liquid form that may be mixed with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds are preferably dissolved or suspended in suitable liquids, such as in buffered salt solution. In addition, stabilizers may be added.

In addition to being provided in a liquid form, for example in gelatin capsule or other suitable vehicle, the pharmaceutical preparations may contain suitable excipients to facilitate the processing of the active compounds into preparations that can be used pharmaceutically. Thus, pharmaceutical preparations for oral use can be obtained by adhering the solution of the active compounds to a solid support, optionally grinding the

resulting mixture and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets or dragee cores.

Suitable excipients are, in particular, fillers such as sugars, for example lactose or sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, as well as binders such as starch, paste using for example, maize starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose, and/or polyvinyl pyrrolidone. If desired, disintegrating agents may be added such as the above-mentioned starches and also carboxymethyl-starch, crosslinked polyvinyl pyrrolidone, agar, or algenic acid or a salt thereof, such as sodium alginate. Auxiliaries are, above all, flow-regulating agents and lubricants, for example, silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragee cores are provided with suitable coatings which if desired, are resistant to gastric juices. For this purpose, concentrated sugar solutions may be used, which may optionally containing gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures. In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations such as acetylcellulose phthalate or hydroxypropylmethyl-cellulose phthalate, are used. Dye stuffs or pigments may be added to the tablets or dragee coatings, for example, for identification or in order to characterize combinations of active compound doses.

Suitable formulations for intravenous or parenteral administration include aqueous solutions of the active compounds. In addition, suspensions of the active compounds as oily injection suspensions may be administered. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension include, for example, sodium carboxymethyl

cellulose, soribitol, and/or dextran. Optionally, the suspension may also contain stabilizers.

The foregoing description details specific methods and compositions that can be employed to practice the present invention, and represents the best mode contemplated. However, it is apparent for one of ordinary skill in the art that further compounds with the desired pharmacological properties can be prepared in an analogous manner, and that the disclosed compounds can also be obtained from different starting compounds via different chemical reactions. Similarly, different pharmaceutical compositions may be prepared and used with substantially the same result. Thus, however detailed the foregoing may appear in text, it should not be construed as limiting the overall scope hereof; rather, the ambit of the present invention is to be governed only by the lawful construction of the appended claims.